The points made in the February 17, 2009 Amendment, the December 30, 2009 Request for Reconsideration, the June 23, 2010 Request for Reconsideration and the previous declarations are incorporated herein.

**QTc Prolongation Cannot Be Predicted from Heart Rate**

The Patent Office persists in arguing that QTc is associated with heart rate (Official Action, page 4, line 16), despite the contrary testimony of both Dr. Seiler and Dr. Savola. The Examiner now relies on newly-cited Funck-Brentano et al., 83 Circulation 536 (1991)(hereinafter "Funck-Brentano") to support her argument that QTc prolongation or its absence can be predicted from heart rate.

The Examiner's attention is directed to the attached Rule 132 declaration by the lead author of Funck-Brentano. Dr. Funck-Brentano states his article does not support the Examiner's position. See paragraph No. 9 of the declaration. Dr. Funck-Brentano also states that QTc prolongation cannot be predicted from heart rate if the correction process is performed appropriately. See paragraph No. 13 of the declaration.

Neither Huupponen et al. or Karjalainen et al. disclose or suggest anything about QTc prolongation or its absence by either atipamezole or fipamezole. In particular, Huupponen et al.'s

disclosure that oromucosal administration of atipamezole did not change heart beat utterly fails to disclose or suggest *anything* regarding possible QTc prolongation to one of ordinary skill in the art. See paragraph No. 12 of Dr. Seiler's declaration, see paragraph Nos. 10-12 of Dr. Savola's second declaration and see paragraph Nos. 9-13 of Dr. Funck-Brentano's declaration.

**The Patent Office Has Improperly Used Hindsight**

It is improper to use hindsight knowledge gleaned from the applicants' specification as prior art:

> To imbue one of ordinary skill in the art with knowledge of the invention...when no prior art reference or references...convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein theat which only the inventor taught is used against its teacher.

W.L. Gore and Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983). See also KSR International Co. v. Teleflex Inc., 550 U.S. 398 (2007)("A factfinder should be aware...of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.")

Both Huupponen et al. and Karjalainen et al. utterly fail to disclose or suggest that oral administration of fipamezole will prolong QTc, or that oromucosal administration of fipamezole will

not prolong QTc. There is simply no disclosure whatsoever of QTc or QTc prolongation in either reference. Instead, the applicants discovered oral administration of fipamezole prolongs QTc. They subsequently discovered oromucosal administration of fipamezole does not prolong QTc. This information is disclosed *for the first time* in the applicants' specification.

The Patent Office improperly takes this knowledge - gleaned from the applicant's specification - to reject the claims. This is a classic case of hindsight error.

The Patent Office compounds its hindsight error by failing to compare the claimed method against the closest prior art to determine whether the claimed method exhibits unexpected results. The closest prior art is Karjalainen et al., which teaches oral administration of fipamezole - the same compound required by the claimed method. Yet the Patent Office erroneously compares the claimed method to Huupponen et al., which is limited to a different compound.

The Patent Office presumption that atipamezole and fipamezole have similar QTc properties is unreasonable. QTc prolongation is so unpredictable it must be separately and empirically determined

for each compound, even if structurally similar. See paragraph 12 of Dr. Seiler's declaration.

**The Surprising Absence of QTc Prolongation When Fipamexole is Oromucosally Administered Renders the Claimed Method Patentable**

The record demonstrates QTc prolongation is a serious side effect which normally will require abandonment of an otherwise promising drug candidate. Moreover, the testing required by the FDA is evidence that a compound's tendency to prolong QTc cannot be predicted, but instead must be empirically determined. The record also demonstrates that those of ordinary skill in the art believe the mechanism of QTc prolongation is based on electrochemical modification of the action potential, and not on a particular administration route of the drug.

Huupponen and Karjalainen both fail to disclose or suggest whether fipamezole will prolong QTc. Instead, the applicants discovered the QTc prolongation problem associated with oral administration of fipamezole.

One of ordinary skill, once aware that oral administration of fipamezole causes dose-dependent QTc prolongation, would reasonably expect oromucosal administration to prolong QTc as well because the particular administration route is not believed to cause QTc.

Moreover, he would believe oromucosal administration of fipamezole would cause an equivalent or longer QTc prolongation than oral administration in view of Huupponen's teaching regarding the increased bioavailability of atipamezole (a fipamezole analog) when oromucosally administered. The unexpected and surprising absence of QTc prolongation when fipamezole is oromucosally administered - in stark contrast to its tendency to prolong QTc when orally administered - overcomes any *prima facie* case of obviousness raised by the cited references.

Reconsideration and withdrawal of the obviousness rejection of claims 23, 25-29 and 31-33 over Huupponen et al. in view of Karjalainen et al. are respectfully requested.

The 35 U.S.C. § 103(a) rejection of claims 23 and 25-33 over Huupponen and Karjalainen, further in view of U.S. Patent No. 6,413,988 to de Proost, is traversed for the reasons previously discussed. De Proost is not directed to $\alpha_2$-adrenergic receptor antagonists, and does not disclose any information concerning oromucosal vs. oral administration of fipamezole. Accordingly, the additional disclosure of this secondary reference does not detract from the unexpected and surprising result achieved by the claimed method of administration. Reconsideration and withdrawal of the

obviousness rejection of claims 23 and 25-33 over Huupponen and Karjalainen, further in view of de Proost, are respectfully requested.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of the obviousness rejections of claims 23 and 25-33, and issuance of a Notice of Allowance directed to those claims, are requested. The Examiner is urged to telephone the undersigned should she believe any further action is required for allowance.

The Extension of Time fee is being paid electronically today. It is not believed any additional fee is required for entry and consideration of this Request. Nevertheless, the Commissioner is authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

/James C. Lydon/

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Declaration Pursuant to 37 C.F.R. § 1.132